Reviewer's report

Title: Epithelial Notch signaling is a limiting step for pancreatic carcinogenesis.

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Reviewer: Florencia McAllister

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In this study, the authors inhibited Notch signaling specifically in the pancreatic epithelial compartment using a dominant negative form of MAML (DNMAML) on genetically engineered mice that express mutant Kras. The authors show that inhibition of epithelial Notch signaling results in delayed pancreatic tumorigenesis at early time points (15 weeks) but the effect is lost at later time points (26 weeks). At the same time, it was noted that Notch signaling inhibition was only transient.

Major compulsory revision

(1) Relevance of Notch signaling in the epithelial pancreatic compartment is the novel aspect of the manuscript. Therefore, validation of the Notch signaling inhibition should be performed by analyzing expression of Notch target genes in mRNA extracted from epithelial cells rather than in mRNA from whole tissue (Figure 2C). An alternative method may consist on quantifying Hes1 protein expression in the epithelial compartment on the immunofluorescence pictures (Figures 2A and 2B).

(2) The genetically engineered mouse model used only causes transient Notch inhibition (achieved at 15 weeks but lost at 26 weeks). Therefore, the temporary delay in pancreatic carcinogenesis at 15 weeks that is not observed at 26 weeks may likely be reflecting the transient effect of the Notch inhibition in the model. Given this particularity, an additional analysis might be required to show more definitive evidence supporting the conclusions. One option may consist on analyzing a larger cohort of mice and perform a sub-analysis of KC and KC;DNMAML mice with transient inhibition of Notch vs mice with prolonged inhibition of Notch and see if they differ in PanIN progression.

(3) Statistical analysis should be performed to aim the interpretation of results (particularly in Figure 2C and 4C).

Minor Essential Revisions

(1) In page 13 of main manuscript (Line 346), please correct “inducer” for “induce”.

(2) Figure 4B- DNMAML 2 weeks picture may not be representative as it does not include acinar clusters.
Discretionary Revisions

(1) Comment on the potential compensatory signaling pathways.
(2) Detail timing/frequency of the caerulein injections

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.